

## International Life Sciences Institute

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*Executive Director*

May 18, 1998

Dr. C. W. Jameson  
National Toxicology Program  
Report on Carcinogens  
7900 Alexander Drive  
Building 4401, Room 3127  
Research Triangle Park, NC 27709

RE: NTP's Call for Public Comments; Agents, Substances, Mixtures and Exposure  
Circumstances Proposed for Listing in or Removing From the Report on  
Carcinogens, Ninth Edition

Specific Comments Regarding Sodium Saccharin

Dear Dr. Jameson:

On behalf of the North American Branch of the International Life Sciences Institute's (ILSI N.A.) Saccharin Technical Committee, we are pleased to provide comments on the National Toxicology Program's proposed delisting of sodium saccharin from the "Report on Carcinogens, Ninth Edition."

The ILSI N.A. Saccharin Technical Committee was formed in 1983 to examine questions concerning the safety of saccharin and its salts. This Committee has worked closely with notable scientists from academia and government as well as from the private sector. In particular, the Committee has sponsored an extensive research program over the past 15 years that has contributed a great deal of knowledge in understanding the mechanisms that underlie the observance of bladder tumors in male rats administered high doses of sodium saccharin. Most of this research has been carried out by Dr. Samuel Cohen and his team of investigators at the University of Nebraska Medical Center.

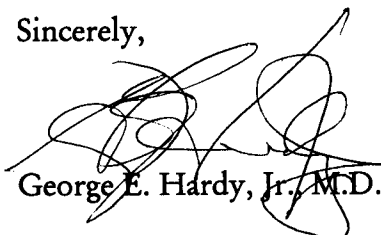
Dr. Cohen's research program has provided a thorough and thoughtful approach to unraveling a very complex problem. Throughout this research, hypotheses have been generated, methodically tested, and when necessary refined. What has resulted from this effort is a biologically plausible mechanism for why sodium saccharin produces tumors in the male rat bladder and at no other site. We believe that this research program is a good example of how mechanistic data can be incorporated into the hazard identification and risk assessment process. A list of Dr. Cohen's major publications on saccharin research that were supported, in part, by ILSI N.A. is attached for your reference.

The scientific data generated by Dr. Cohen and others provide compelling evidence that the occurrence of bladder tumors in male rats fed high doses of sodium saccharin can be explained mechanistically in terms that are simply not relevant to humans. As Dr. Cohen has shown, carcinogenicity of saccharin is specific to the male rat and requires high doses of the sodium salt which produce a precipitate in the urine. This urinary precipitate requires specific conditions for it to form. These conditions include a pH of 6.5 or greater, a relatively high concentration of calcium and phosphate, a high urinary protein concentration, and an overall concentrated urine with a relatively high osmolality. The precipitate, in turn, is cytotoxic to the urethelium, and results in a regenerative hyperplasia that, if it persists, leads to the formation of tumors. Administration of high doses of other sodium salts produces similar effects.

As a result of the extensive body of research he and others have conducted, Dr. Cohen has written, "Therefore, there is likely to be no carcinogenic hazard associated with human consumption of these sodium salts [including sodium saccharin]..." [Capen, C.C., Dybing, E., Rice, J.M. & Wilbourn, J.D., eds (1998) *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis*. Cohen, Samuel M. *Calcium Phosphate-Containing Urinary Rat Bladder Carcinogenesis*. IARC Scientific Publications No. 147. Lyon, (in press)] In addition, in a recent presentation, Cohen summarized this issue by stating, "In summary, mechanistic considerations suggest that the urinary bladder tumorigenic response to sodium saccharin requires high doses and is rat specific. The lack of effect in mice and more importantly in monkeys, combined with strong epidemiologic evidence from humans and our understanding of mechanism, strongly support the conclusion that exposure to saccharin does not pose a carcinogenic risk to humans." (Cohen, Samuel M., *Saccharin Safety Update*, Low-Calorie Sweeteners, Proceedings of a Seminar in India, February 5-6, 1997, New Delhi, India.)

The National Toxicology Program is charged with identifying and listing substances that are either "known to be human carcinogens" or "may reasonably be anticipated to be human carcinogens." Under these circumstances, the existing scientific data base supports the removal of sodium saccharin from the NTP Annual Report on Carcinogens. We trust that the National Toxicology Program will give serious consideration to the important mechanistic data on saccharin during its deliberations.

Sincerely,

A handwritten signature in black ink, appearing to read "George E. Hardy, Jr.", with a stylized, cursive script.

George E. Hardy, Jr., M.D.

PARTIAL LIST OF PUBLICATIONS FROM RESEARCH FUNDED IN PART  
BY THE ILSI N.A. SACCHARIN TECHNICAL COMMITTEE

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Cano, M., Suzuki, T., Cohen, S.M. Application of SEM and x-ray analysis of urinary tract cancer in animals and humans. *Scanning Microscopy.* 17:365-372, 1993.

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